Remarks

The above Amendments and these Remarks are in reply to the Office Action mailed November 12, 2008.

Claims 1-6 and 8-30 were pending. Claims 3-6, 13-18 and 22-24 were withdrawn in the prior REPLY in response to a restriction requirement.

A Petition for Extension of Time for two (2) months, and the appropriate fee are included with this REPLY.

Claim Objections

The Examiner objected to the claims for typographical errors in Claim 2. Applicants have herein amended Claim to correct the spelling of the words "phospholipase" and "protein."

Claim Rejections Under 35 U.S.C. §112, first paragraph

Claims 1, 2, 8-12, 19-21 and 25-30 stand rejected under 35 U.S.C. §112, first paragraph for not defining "cystanin SN" or "cystatin SN peptide." Applicants have amended the claims to include the limitation that the markers used have the sequence of SEQ ID NO:108. Support for this amendment can be found in the specification at least at page 79, line 9. Applicants also note that the term "cystatin SN" means "CST1," that "cystatin SA" means "CST2," and that "cystatin S" means "CST4." These definitions are provided in the application as filed at least on pages 6 and 7.

Claim Rejections Under 35 U.S.C. §102

Claims 1, 2, 8-12, 19-21, 25-27, 29 and 30 stand rejected under 35 U.S.C. §102(e) as anticipated by US 2004/0076955 (the '955" publication).

According to the Examiner, the 955 "publication discloses a method of diagnosing a **colon, small intestine and large intestine disorder** comprising identifying and comparing diagnostic markers listed in Tables 1A-13 including cystatin SN..." Office Action, page 5, paragraph 7; emphasis added.

Applicants respectfully submit that the 955 publication is drawn to methods of diagnosing cancers different from gastric cancer, and therefore that the 955 publication cannot anticipate Applicants' claimed invention.

Claims 1, 19 and 27 stand rejected under 35 U.S.C. §102(a) as anticipated by Utsunomiya et al ("Utsunomiya"). According to the Examiner, Utsunomiya discloses "a method of detecting the expression of cystatin-like metastasis=associated protein (CMAP) in **colorectal tumor**..." Office Action, page 6, paragraph 8; emphasis added.

Applicants respectfully submit that the marker used "CMAP" is not a "cystatin SN protein or cystatin SN peptide." Additionally, Utsunomiya does not provide any method for diagnosis of gastric cancer, as in Applicants' claimed invention.

Additional support for this view is provided by the Declaration of Parry John Guilford, attached hereto as Exhibit 1. In particular, "**none of the prior art discloses the subject matter claimed** in this application **and** therefore that the **uses of the claimed markers for detection of gastric cancer are novel**. This opinion is based on the fact that the references cited in the Office Action do not disclose the use of the claimed markers for detection of gastric cancer." Guilford Declaration, paragraph 12; emphasis added

Rejections Under 35 U.S.C. §103

Claims 1, 2, 8-12, 19-21 and 25-30 stand rejected under 35 U.S.C. §103(a) as obvious over the 955 publication and further in view of US 2006/0019256 (the "256 publication").

Applicants respectfully submit that the 755 publication cannot render Applicants' claims obvious because the types of cancer detected (colon, large intestine and small intestine) are not the same as gastric cancer as in Applicants' claims. The Examiner has provided no rationale why a person of ordinary skill would consider markers for gastric cancer to be the same as or predictive of colon, large intestine, small intestine cancers, xenograft tumors or cancer stem cells.

Support for this view is provided by the Declaration of Parry John Guilford, Ph.D. A true copy of this Declaration is attached to this REPLY as Exhibit 1. In particular, "persons of skill in the art would not be able to identify particular marker profiles for previously unstudied diseases without actual experimentation. This opinion is based on the lack of predictability of particular markers being useful for detecting unrelated cancers. Not all cancers have the same profile of markers. Therefore, use of markers may be successful in detecting cancer in breast tissue, stem cells, xenograft tumors, colon cancer, large intestinal cancer, or small intestinal cancer yet would not be successful in detecting other cancers, including gastric cancer without direct experimentation." Guilford Declaration, paragraph 13.

The Examiner admits "publication '19256 teaches characterizing and diagnosing cancer, for example **colon carcinoma** comprising identifying tumor cancer markers, such as SERPINB5 ... and SERPINH1. ... It would have been prima facie obvious to one of ordinary skill in the art at the time, to include these additional cancer markers. One would have been motivated to use these particular markers because the secondary reference teaches these markers' upregulated expression is **consistent with** solid tumors, such as **colon carcinoma and breast cancer**." Office Action, page 7, paragraph 10; emphasis added.

Applicants submit that to make a *prima facie* case for obviousness, there has to be more teaching than merely being "consistent with." Applicants respectfully suggest that a person of ordinary skill would not have necessarily viewed SERPINB5 or SERPINH1 to be necessarily diagnostic of all solid tumors, and would not

necessarily be diagnostic of gastric cancer in particular.

Claims 1, 2, 8-12, 19-21 and 25-30 stand rejected under 35 U.S.C. §103(a) as obvious over WO 03/067916, in view of the 955 and 256 publications. According to the Examiner, "WO 03/057916 teaches a method of detecting the level of expression of cancer markers in biological samples, including plasma, fluids and the like by **immunohistochemistry** methods... The expression profiles of a number of **xenografts** including **colon** samples. ... **The WO document does not teach the specific gastric tumor makers listed in claims 1 and 2.**" Office Action, page 8, paragraph 10; emphasis added.

Applicants respectfully submit that immunohistochemical methods as described are not accurate enough to quantify actual expression levels of marker proteins. Further, Applicants submit that xenograft colon tumors in experimental animals are not necessarily predictive of human gastric cancers. In particular, "persons of skill in the art would not be able to identify particular marker profiles for previously unstudied diseases without actual experimentation. This opinion is based on the **lack of predictability of particular markers being useful for detecting unrelated cancers**. Not all cancers have the same profile of markers. Therefore, use of markers may be successful in detecting cancer in breast tissue, stem cells, xenograft tumors, colon cancer, large intestinal cancer, or small intestinal cancer yet would not be successful in detecting other cancers, including gastric cancer without direct experimentation." Guilford Declaration, paragraph 17.

Applicants respectfully submit that there is insufficient evidence to make a valid *prima facie* case for obviousness. Under Supreme Court precedent (*Graham v. John Deere*, *KSR v. Teleflex*), a *prima facie* case for obviousness requires analysis of 4 "Graham" factors:

1. Scope and contents of the prior art;
2. Differences between the prior art and the claimed invention;
3. Level of ordinary skill in the art; and
4. Secondary indicia of non-obviousness.

Further, in the chemical and pharmaceutical arts, the Federal Circuit case of *Pfizer v. Apotex* provides guidance. In particular, *Pfizer* provides limits on what would be expected of a person of ordinary skill to "try."

Applicants provide the following comments relating to the Graham factors.

1. Scope and contents of the prior art

The prior art contains descriptions of several markers identified as being diagnostic of colon cancer, large intestine cancer, small intestine cancer and breast cancer. The prior art also includes knowledge of immunological methods for detecting proteins, including general Western blotting methods.

However, none of the cited art discloses or teaches any relationship between any of the published markers and gastric cancer. Support for this assertion is provided by the Declaration of Parry Guilford. In particular, "the prior art teaches use of some markers useful for detecting certain cancer types, including colon cancer, large intestine cancer, small intestine cancer, breast cancer, xenografted tumors and cancer stem cells. However, **the cited references do not teach use of those markers in the detection of gastric cancer.**" Guilford Declaration, paragraphs 13 -14.

2. Differences between the prior art and the claimed invention

As admitted by the Examiner, none of the citations describe markers of gastric cancer. Unlike the prior art, Applicants' claims are directed toward methods for detecting gastric cancer. Thus, the differences between the prior art and the instant claims is very large. The 955 and other publications disclose thousands of markers that could **potentially** be used to diagnose gastric cancer. However, the cited references provide no guidance as to ***which*** of the many thousands of markers should be used or even tried to diagnose gastric cancer.

Applicants respectfully submit that a *prima facie* case for obviousness must be based on more than an "obvious to try" thousands of alternatives. In *Pfizer v. Apotex*, the Federal Circuit held claims to a formulation of a known drug and a particular salt, the besylate salt, was invalid as obvious because the person of ordinary skill would have been motivated to "try" all 53 of the then-known and FDA-approved salts.

The situation in the instant application is much more complex that that in *Pfizer*. Confronted with a huge number of potential tumor markers, a person of ordinary skill would have to decide which of thousands of potential markers should be "tried." Applicants submit that based with such a daunting task, a person of ordinary skill would not have sufficient guidance to select which markers to "try" and therefore, Applicants submit that there is a substantial defect in the *prima facie* case for obviousness.

Further support for this view (lack of a sufficient *prima facie* case of obviousness) is provided by the Guilford Declaration. In particular, "the differences between the instant invention and the prior art is too large to be overcome by a person of ordinary skill in the art at the time the application was filed using only routine methods. A person of skill in the art **would not be able to select from among the thousands of potential markers and select those that are applicable to a newly studied cancer type.**" Guilford Declaration, paragraph 18.

Next, through a process of trial and error, Applicants unexpectedly found certain specific markers are useful in detecting gastric cancer. Tests directed toward use of these markers are the subject of the pending claims in this application. Applicants submit that the differences between the prior art and the claimed invention are so large that the person of ordinary skill would not have been able to predict the power of discrimination of gastric canter from non-tumor tissue. "Additionally, the instant application discloses unexpected features of the claimed markers. We found that the markers, cystatin 1,2 &4 (CST 1,2 &4), are

expressed in gastric tumor tissue with **over 25,000 fold maximal expression compared to non-tumor tissue** (FIG. 3). FIG 5(b) also demonstrates a totally unexpected finding, that **CST 1,2 &4 can completely separate gastric tumor tissue from non-tumor tissue**. Similar unexpected findings are reported for LOXL2 (FIG. 5(f)), SFRP4 (FIG. 5(h)), SPARC (FIG. 5(i)), SPP1 (FIG. 5(j)), THBS2 (FIG. 5(k)), and TIMP1 (FIG. f(l)). **These degrees of separation of gastric tumor tissue and non-cancerous tissue is totally unexpected based on the prior art** and such unexpected results would not be apparent to a person of skill in the art based on tumors in other tissues.

For single marker analysis, Applicants demonstrated that of 29 possible tests for gastric cancer using only a single marker, two (2) tests showed greater than 90 % sensitivity, and one test showed more than 95% sensitivity (FIG. 13).

For double marker analysis, Applicants demonstrated that of a possible 406 such combination tests, 33 showed greater than 90% sensitivity, 27 showed greater than 95% sensitivity and one showed greater than 99% sensitivity (FIG. 13).

For triple marker analysis, of the possible 3654 tests, 796 showed greater than 90% sensitivity, 457 showed greater than 95% sensitivity and 50 triple marker tests showed greater than 99% sensitivity. Applicants respectfully submit that unprecedented degrees of sensitivity in detecting gastric cancer were well beyond the ordinary skill in the art until the disclosure in the instant application.

Applicants also demonstrated very high degrees of separation of gastric tumor from non-tumor tissue using methods for detecting marker proteins. FIG. 14 shows comparisons of protein levels of SPARC, CST1, IGFBP7 and THBS2 in tumor tissue (T) and non-tumor tissue (N). For SPARC and CST 1, high expression levels were found in tumor tissue, but were very low or undetectable in non-tumor tissue. This finding demonstrates that Applicants' invention as currently claimed provide very high sensitivities of separation of gastric tumor from non-tumor tissues.

3. Level of Ordinary Skill

Applicants submit that the level of skill in the art is high, and that workers typically have advanced scientific degrees and experience in laboratory work.

However, Applicants submit that the ordinary level of skill is insufficient, because knowledge of the particular markers that would be useful for detecting gastric cancer was not known prior to the instant application. Further, although the level of skill is high, the precise identification of markers useful for detecting gastric cancer could not be predicted based on the prior art. Previous to the instant application, markers useful for detection of gastric cancer were not known. Only with the instant disclosure does the art now have an understanding of molecular markers useful for diagnosis of gastric cancer, and provide a degree of certainty regarding diagnosis.

Applicants also submit that the person of ordinary skill do have knowledge about which markers are useful for diagnosing certain tumor types (e.g., colon, large intestine, small intestine), but that knowledge does not imply sufficient expertise to know which of those thousands of markers would be useful for diagnosis of gastric cancer. Moreover, Applicants respectfully submit that the detailed level of analysis of use of single, double and triple marker tests to detect gastric cancer could not have been carried out by persons of ordinary skill in the absence of the complex and multi-faceted methods disclosed.

4. Secondary Indicia of Non-Obviousness: Unexpected Properties

In addition to the three "Graham" factors discussed above, Applicants specification demonstrates "Secondary Indicia of Non-Obviousness." In particular, Applicants have discovered truly unexpected properties of the disclosed methods. Even if cystatin SN protein or cystatin SN peptide might be worth trying to use for detecting gastric cancer, the totally new and unexpected sensitivity of detection of gastric cancer provided by measuring cystatin SN expression was not appreciated and could not have been previously appreciated. As noted above, the difference in expression levels of over 25,000 in gastric tumor compared to non-tumor tissue was completely unexpected. Further, the fact that cystatin SN expression levels provide complete separation gastric tumor tissue from non-tumor tissue (e.g., see FIG. 5(b)) means that for the first time, a simple method can be used to accurately distinguish gastric cancer tissue from non-tumor tissue.

Additional unexpected properties were found for certain other gastric cancer markers used singly. For example, measurement of expression of LOXL2 (FIG. 5(f)), SFRP4 (FIG. 5(h)), SPARC (FIG. 5(i)), SPP1 (FIG. 5(j)), THBS2 (FIG. 5(k)), and TIMP1 (FIG. f(l)) provide substantial separation of tumor from non-tumor tissue. These degrees of separation of gastric tumor tissue and non-cancerous tissue is totally unexpected based on the prior art and such unexpected results would not be apparent to a person of skill in the art based on tumors in other tissues.

In addition to the value of the single markers described herein above, Applicants also unexpectedly found that very high sensitivity can be obtained using two, three or more markers together. Use of multiple markers to increase sensitivity of diagnosis was not described in any of the prior art references, and especially was not provided for detection of gastric cancer. Applicants' new tests provide for the first time, sensitivities of diagnosing gastric cancer that are substantially greater than for any prior art test for this tumor type. As a result of Applicants' invention, tests having sensitivity of greater than 90 %, greater than 95% or even greater than 99% are possible now for the first time. Such sensitivity of tests for detecting gastric cancer are totally new and completely unexpected based on the prior art.

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Conclusions

Applicants respectfully submit that the rejections under 35 U.S.C. §112, first paragraph, and 35 U.S.C. §102 have been overcome. Further, Applicants submit that there is insufficient evidence presented to make a *prima facie* case for obviousness under 35 U.S.C. §103. Even if there were a *prima facie* case for obviousness, Applicants have overcome that *prima facie* case by providing evidence in the application as filed for completely unexpected and clinically beneficial results. Therefore, Applicants request the Examiner to reconsider the rejections and to find the claims allowable.

Please note that the Attorney and Correspondence Address have changed. A new Power of Attorney was filed with and accepted by the USPTO. For the Examiner's convenience, the new information is provided below.

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A Petition for Extension of Time of two (2) months and the required fee are included herewith.

The Examiner is respectfully requested to telephone the undersigned if he can assist in any way in expediting issuance of a patent. The Commissioner is authorized to deduct from or refund funds to Deposit Account 50-4089 for any additional fee related to this Reply.

Respectfully submitted,

Date: April 2, 2009 By: D. Benjamin Borson

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